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Plant Molecular Farming: Issues and Challenges for Canadian Regulators

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Acronyms

CFIA	Canadian Food Inspection Agency
APHIS	Animal and Plant Health Inspection Service
PBO	Plant Biosafety Office
BIO	Biotechnology Industries Organization
CGB	Commission du génie biomoléculaire
CGG	Commission du génie génétique
EMEA	European Agency for the Evaluation of Medicinal Products
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GMO	Genetically Modified Organism
USDA	United States Department of Agriculture
PNT	plants with novel traits

Executive Summary

Plant molecular farming (PMF) or "biopharming" is a technique in which molecules of pharmaceutical or industrial value are produced by genetically manipulated or modified (GM) plants. It represents the "third generation" of plant genetic modifications. The first generation manipulated plants for pesticide and insect resistance while the second aimed to improve their agronomic characteristics (e.g. cold and drought tolerance) and nutritional characteristics. This research report focuses more specifically on the production of drugs through the use of GM plants.

PMF is an emerging industry in Canada. PMF appears to offer economic and technical advantages for pharmaceuticals production, including lower production costs in comparison with conventional methods and safer products for the consumer. But of course, no new technology is risk-free, and PMF is no exception. There are legitimate concerns as to the impacts of PMF on human and animal health and the environment. Since some of the plants used are field crops, there is the worry that the food chain could become contaminated by pharmaceuticals. The Canadian Food Inspection Agency is currently attempting to regulate PMF by laying down guidelines for field trials. These regulations must be proactive in order to satisfy the demands of the industry and the public for clear, rigorous and transparent legislation in this area.

The government of Canada and the biotechnology industry have numerous challenges to overcome. Of particular importance is an information strategy for consumers, who do not know enough about this new drug production technique to be able to understand its risks and benefits.

After having examined the various issues raised by plant molecular farming, Option consommateurs puts forward the following recommendations. These recommendations should be read in conjunction with the sections to which they relate.

Section 2.0: Plant Molecular Farming Regulation in Canada

RECOMMENDATION 1:

Option consommateurs recommends that applications for authorization of field trials be reviewed and commented on by an independent committee of experts, not only by the CFIA.

RECOMMENDATION 2:

Option consommateurs recommends that guidelines for plant molecular farming in confined spaces (greenhouses and mines, for example) be developed by the CFIA without delay.

RECOMMENDATION 3:

Option consommateurs recommends that the CFIA mobilize a sufficient number of inspectors in the field to supervise and monitor molecular farming trials.

Section 5.3: Is Molecular Farming Profitable?

RECOMMENDATION 4:

In view of the lack of adequate data on the commercial viability of molecular farming, Option consommateurs recommends that the CFIA conduct a study on its economic impacts, and more specifically on the cost of drugs derived from this technology.

Section 6.0: Risks of Molecular Farming

RECOMMENDATION 5:

Given the excessive risk of contamination of the food chain by plant-based pharmaceuticals, Option consommateurs recommends that PMF not be performed by farmers under contract, but only by adequately trained biotechnology company staff.

RECOMMENDATION 6:

Option consommateurs recommends that more scientific research be done on molecular farming, more particularly on the issues related to long-distance pollination, gene transfer and impacts on non-target organisms.

RECOMMENDATION 7:

Option consommateurs recommends that all production platforms be rigorously studied on a case-by-case basis before their environmental release and that isolation perimeters and strict physical and genetic confinement techniques be put in place.

RECOMMENDATION 8:

Given the risk of contamination of the food chain by biopharmed plants and the hermeticity problems of the current system, Option consommateurs strongly recommends that food crops be excluded from the production of pharmaceutical biomolecules, except under strict confinement.

RECOMMENDATION 9:

To prevent contamination of food and feed, Option consommateurs recommends the development, without delay, of guidelines for robust identification and traceability systems for plants and products derived from PMF.

Section 7.0: Views of Farmers and Consumers on PMF

RECOMMENDATION 10:

Given the lack of publicly available information about plant molecular farming and the concomitant lack of consumer knowledge of the issues, Option consommateurs recommends that the Government of Canada implement an information strategy based on the most recent work in the field of PMF.

RECOMMENDATION 11:

Option consommateurs recommends that the information provided to the public by the Government of Canada on molecular farming be evaluated by an independent interdisciplinary committee before being made public.

RECOMMENDATION 12:

Option consommateurs recommends that the public agencies whose mandate is to provide scientific information to the public, such as the Conseil de la science et de la technologie du Québec, be involved in a public information and awareness strategy on plant molecular farming.

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Introduction

Plants have long been the principal source of medicinal drugs. Today, about 57% of the 150 best-known drugs contain at least one major active ingredient originally extracted from a plant (Grifo et al., 1997). Over time, scientists have identified many human proteins and the genes that code for their production. Proteins are the human body's defence against disease. They are typically synthesized by modified bacteria, mammal and insect cells, yeasts and, more recently, in genetically modified (GM) plants. The technique consists in transferring a specific gene into plant cells. The production of pharmaceuticals by plants — called "plant molecular farming" (PMF) or "biopharming" — represents the third generation of agricultural biotechnologies. The first generation manipulated plants for insect and pesticide resistance, while the second modified plants to improve their agronomic characteristics (e.g., drought- and cold-tolerance) and their nutritional characteristics (e.g., high-lysine corn).

PMF poses numerous technical and economic challenges for the Canadian regulatory system as well as biotechnology and pharmaceutical companies using this method. This research report deals with the benefits and risks of PMF as regards drug production. In section 1, we review the definition and application of molecular farming, considering the plant species involved and the biopharmaceuticals synthesized. In sections 2 to 4

we discuss the regulatory frameworks for PMF in Canada, the United States and France. In section 5 we consider the technical and economic benefits of PMF. In section 6 we enumerate and explain the risks to human and animal health and the environment potentially engendered by this practice, and also address the methods available to attenuate these risks. Finally, in section 7, this report presents the opinions of farmers and consumers on this new technology.

1.0 Plant Molecular Farming (PMF): Definition and Application

The Canadian Food Inspection Agency (CFIA) defines PMF as "the use of plants in agriculture to produce biomolecules instead of food, feed and fibre. Plants with introduced novel traits that produce scientifically, medically or industrially interesting biomolecules are grown as crops and harvested for the biomolecules."[1]

Many types of substances can be obtained from GM plants used in PMF:

- **Primary products**: Antibodies, antibody fragments, enzymes (industrial, therapeutic, diagnostic, cosmetic), structural proteins, antigens (vaccines), therapeutic agents, drugs, enzyme inhibitors.
- **By-products**: Bioplastics, vitamins, cofactors, nutraceutics, secondary metabolites (phenolic compounds, glucosinolates, tannin, starches, sugars, perfumes, scents and aromas, alkaloids), fibres.

In this report, we focus more specifically on the issues surrounding the use of molecular farming to produce antibodies, vaccines, and other pharmaceuticals. Antibodies are the product whose production is likely to undergo the greatest increase in the coming years.

In PMF, after scientists have identified a useful protein and understood its function, they insert the genes that code for the protein into the cells of a plant. As the plant grows, it reproduces the protein, which is extracted after harvest. Currently, at least 350 plants that are genetically modified to produce pharmaceuticals are under clinical development in Canada and the United States (Stephen, 2001). The literature refers to some 34 proteins synthesized by plants, including antibodies (called "plantibodies" in the new language of PMF), blood proteins such as albumin and hemoglobin, enzymes, hormones such as erythropoetin and immunogenic proteins for vaccination, such as rabies glycoprotein (Faye et al., 2001). No plant-based pharmaceuticals have been put on the market as yet. Clinical trials are the most advanced stage of development for any substance.

1.1- Plants Used in PMF

The first PMF experiments used corn and tobacco; corn because it easy to grow, and tobacco because it lends itself well to genetic manipulation, produces abundant seeds, and has large leaves that represent a great deal of biomass. Other plants used include canola, rice,[2] safflower, soy, alfalfa, and potato. There is nothing random about this choice of plants; they were selected for their known properties conducive to biotechnological research, as well as the wealth of existing knowledge about their pollination, genetics, seed dormancy and weediness potential. This information is crucial in determining pollen movement and the possibility of gene transfer with conventional plants. All this information is used in order to achieve maximum isolation of field trials (Felsot, 2002).

In Canada, the main plants used in PMF are safflower, tobacco and alfalfa.

1.2- PMF in Canada: An Emerging Industry

PMF represents a new business opportunity for Canada. The pharmaceutical biotechnology industry is developing very rapidly and building increasingly close ties with the agricultural sector. The current technology used in the production of certain drugs apparently no longer suffices, to the extent that some of them could become unavailable if more efficient, less costly production systems are not put in place. Thus, it is the constraints of today's pharmaceutical production that are stimulating the creation of the new PMF industry. Biopharming appears to offer unique advantages for the production of pharmaceutical proteins. The industry sees it as an excellent opportunity to position Canada as an important player in the biotechnology industry, produce high-value crops, build pharmaceutical plants, inject funds into the rural economy, and develop related industries. Biopharming also makes for lower-cost drug production and offers

[1] Definition taken from CFIA website at http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_faqe.shtml
[2] Wheat and rice have an advantage over other plant species in that they do not produce harmful compounds such as alkaloids (Stöger et al., 2000).

better product safety.[3] The benefits of PMF are discussed in further detail in section 6.2 of this report.

1.3- PMF Leaders

Many of the world's biotechnology companies are taking a keen interest in the potential of PMF. The list below is not exhaustive, but does include the main players in this field and the products they are currently researching.

Canada

- Medicago (Québec): alfalfa leaves for hemoglobin production.
- Sembiosys Genetics (Calgary): safflower for production of a fat-fighting peptide and somatotrophin.
- Plantigen (Ontario): trials of several plants for protein production.

United States

- AtlaGen Bioscience (Morgan Hill, CA and Richland, WA): potato leaves.
- Ventria Bioscience: potato tubers.
- API: rice and other plants.
- CropTech: tobacco leaves for production of uronidase, irunosidase, glucocerebrosidase (for Gaucher's disease) and vaccines.
- Dow AgroSciences: corn for production of vaccines and antibodies to prevent certain animal diseases.
- IPT (Monsanto): corn for antibody and somatotrophin production.
- Epicyte Pharmaceutical (San Diego): corn and rice seeds.

[3] Information taken from a presentation by SemBioSys Genetics inc., 8 May 2001.

- Large Scale Biology (Vacavill, CA): tobacco leaves for development of alpha-galactosidase and drugs to treat non-Hodgkin's lymphoma.
- Phytomedics: (Dayton, NJ): tobacco and tomatoes.
- PlantGenix (Philadelphia, PA): unknown.
- Prodigene (College Station, TX): corn seeds for production of laccase, avidin, beta-glucoronidase and aprotinin.
- Planet Biotechnology (California): tobacco leaves to produce a cavity-fighting mouthwash.
- Monsanto Protein Technologies: corn.
- SubTerra/Prairie Plant Systems: tobacco for production of glycoprotein B to treat human cytomegalovirus (HCMV).

Germany

- Planton: potato tubers.
- Greenovation: corn for production of factor IX for hemophilia B treatment.
- MPB Cologne: potato tubers, canola seeds for production of antibodies to detect waterborne and foodborne pathogens.

France

- Meristem Therapeutics (Clermont-Ferrand): corn seeds, tobacco leaves for production of hemoglobin, gastric lipase, collagen, beta interferon, lactoferrin and albumin.

Switzerland

- Syngenta: antibodies and others.

Denmark

- Cobento Biotech: *Arabidopsis* (weed of the mustard family).

2.0 PMF Regulation in Canada

2.1- Role of the CFIA

The CFIA's Plant Biosafety Office (PBO) is responsible for regulating field trials of plants for use in PMF. Two existing directives may apply to PMF but are not specific or exclusive to it. The first, Regulatory Directive 2000–07, concerns guidelines for the environmental release of plants with novel traits (PNT)[4] in confined field trials,[5] was revised, published, and took effect on 5 February 2002. In April 2003, the PBO announced provisional amendments to directive 2000–07 regarding confined field trials of PNTs for use in molecular farming.[6] Directive 94–08 on assessment criteria for environmental risks associated with PNTs was still under review at the time of writing. Finally, another directive, 95–03 on animal foods derived from PNTs, could in the future be applied to subproducts of molecular farming used for livestock feed.[7]

[4] The PBO is responsible for regulating PNTs in Canada. The CFIA defines PNTs as "plant varieties/genotypes that are not considered substantially equivalent, in terms of their specific use and safety both for environment and for human health, to plants of the same species, having regard to weediness potential, gene flow, plant pest potential, impact on non-target organisms and impact on biodiversity." Biopharmed plants are considered PNTs. For more information, see the CFIA website at http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_come.shtml .

[5] Confinement means "geographical, biological and genetic mechanisms that isolate a PNT from its environment, including isolation from other sexually-compatible plants. Isolation distances and male sterility are examples of confinement." Source: http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_come.shtml .

[6] For details on this modification, see: http://www.inspection.gc.ca/english/plaveg/pbo/dir/dir0007ie.shtml .

[7] Regulatory Directives 95–03, *Guidelines for the Assessment of Livestock Feed from Plants with Novel Traits*, and 94–08, *Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits*, were updated in consultation with representatives of the livestock feeding and agriculture industries, universities, governments, and consumer groups. Comments are being solicited from the Canadian public until 24 July 2003.

From 31 October to 2 November 2001, the CFIA held consultations to cover in detail the issues around regulation of PNT use in molecular farming.[8] Following these consultations, the PBO drafted an amendment to directive 2000–07 with a view to imposing stricter conditions of isolation and inspection of confined research field trials for plant-based production of pharmaceuticals and industrial products. This amendment is separate from the review of directive 2000–07 whose objective is to improve regulation of confined research field trials for PNTs in general. In April 2003, provisional modifications were made to regulatory directive 2000–07 covering all applications of PNT confined field trials of PNT specifically for molecular farming. The government of Canada is currently conducting an overall review of policies affecting PMF in the country. The purpose of the review is to solicit Canadians' views on aspects such as ethics, regional socioeconomic consequences, and impacts of this new technology on international trade. While these procedures are in progress, applications for PNT field trials will be considered on a case-by-case basis. The CFIA will base its development of new regulations on the outcome of the general policy review.

The CFIA claims that it is aware of the potential risks posed by molecular farming. In this regard, the PBO is mandated to assess the potential environmental risks of PNTs before authorizing their environmental release. Currently, the PBO is monitoring two types of release: small-scale confined research field trials on PNTs for which environmental data is lacking, and unconfined release,[9] which is conditional upon a rigorous assessment of all environmental data gathered during the field trials.

Before authorizing confined research field trials, the PBO requires the technology developer to supply information on the new trait and how it is expressed in the plant. Directive 2000–07 and its application form explain the information required for this assessment. Applications are not authorized where the developer is unable to demonstrate

[8] The proceedings of this consultation are on the PBO website at: http://www.inspection.gc.ca/english/plaveg/pbo/pbobbve.shtml .

[9] Unconfined release (or environmental release) is "use without requirements for reproductive isolation, site monitoring or post-harvest land use restrictions. Risk assessment criteria for unconfined release are given in Regulatory Directive 94-08. In certain cases, restrictions are applied to an unconfined release for safe deployment of the PNT." Source: http://www.inspection.gc.ca/english/plaveg/pbo/mf/mf_communique.shtml#A3 .

that the new trait and its mode of expression pose no significant risk in a small-scale confined field trial. There are maximum area criteria for such trials and they are authorized in limited numbers. They are conducted in accordance with specific reproductive isolation criteria under the supervision of the CFIA, with the agency inspecting all confined field trials from start to finish and even after harvest. In this way, the PBO attenuates the potential environmental risks while allowing the developer to collect the data necessary to assess the environmental risk associated with unconfined release. The information required for unconfined release is given in Directive 94–08. The PBO compares the PNT with its unmodified equivalent of the same species. The following characteristics are assessed: weediness potential, cross-pollination capacity, potential impacts on the health of the plant and on non-target species (e.g., soil microorganisms), potential effects on biodiversity.

The developer does not have the opportunity to collect all the environmental data required for unconfined release before a PNT can be planted outdoors under confinement. Nevertheless, the developer must provide detailed and complete molecular and biological information when requesting authorization to proceed with such a trial. The required data relates to the modification itself as well as the fertility, habitat, weediness potential, dormancy, pollen, seed and vegetative propagation, allelopathy, toxicity, and allergenicity of the modified plant and its unmodified counterpart. It must also provide information on the trial site, including the presence of related wild species and endangered species. Finally, it must provide protocols for the use of the site during and after the trial. The PBO evaluates this information and decides whether or not to authorize the field trial, determining the area allowed and the terms and conditions of reproductive isolation so as to reduce environmental exposure to the PNT. The CFIA inspects the field subsequently in order to verify conformity to these terms and conditions. The primary purpose of a confined research field trial is to gather data on the environmental interactions of the PNT for use in assessment during an unconfined field trial.

In summer 2002, prior to the amendment of Directive 2000–07, the CFIA authorized three confined research trials for production of industrial but non-pharmaceutical

molecules. Two of the trials involved tobacco and one involved safflower. The names of the host provinces were disclosed on the CFIA website in advance, giving the corresponding provincial governments the opportunity to comment on or even object to them. Other information, such as the exact location of the trial and the nature of the genetic construction involved, was kept confidential and disclosure was left to the developer's discretion.

As they stand, the Canadian molecular farming regulations are tailored to small-scale field trials and commercial growing. Production in confined areas such as greenhouses is an unregulated domain, which means that biotechnology companies are operating without strict guidelines for this type of production. Clear and transparent Canadian regulations are necessary without delay.

RECOMMENDATION 1:

Option consommateurs recommends that applications for authorization of field trials be reviewed and commented on by an independent committee of experts, not only by the CFIA.

RECOMMENDATION 2:

Option consommateurs recommends that guidelines for molecular farming of pharmaceuticals in confined spaces (greenhouses and mines, for example) be developed by the CFIA without delay.

RECOMMENDATION 3:

Option consommateurs recommends that the CFIA mobilize a sufficient number of inspectors in the field to supervise and monitor molecular farming trials.

2.2- Role of Health Canada

Under the *Food and Drugs Act*, Health Canada is responsible for regulation of animal- and plant-derived biological products (biologics). Where PMF is concerned, Health Canada's role is to assess product safety (defined as toxicity times exposure) from the standpoint of ingestion, inhalation, and topical exposure (accidental or otherwise). The department is also responsible for immunogenicity and allergenicity risks, toxicological risks, and other risks these products may pose. Data that must be reviewed in the case of biologics derived from transgenic plants relate to the drug substance itself (toxicology, stability, quality, purity), efficacy (pharmacokinetics) and the production process (equipment, isolation and safety, good manufacturing practices).

Drugs derived from molecular farming are subject to the same evaluation process as any other drug before being placed on the market, the purpose being to establish their bioequivalence with the product of origin.

3.0 PMF Regulation in the United States

In the United States, the Department of Agriculture (USDA) regulates GM plant trials. The USDA keeps confidential all information on trial sites and products under development. The Food and Drug Administration (FDA) is responsible for regulating drugs extracted from biopharmed plants. As in Canada, GM plant-based pharmaceuticals must go through a panoply of trials including animal toxicity trials, three stages of clinical trials on humans, and post-market surveillance (Merck Manual, 1992).

The USDA, in conjunction with the FDA, produced a document titled "Guidance for industry: drugs, biologics, and medical devices derived from bioengineered plants for use

in humans and animals." This document was put forward for discussion from September 2002 to February 2003. On 6 March 2003, the FDA, the USDA, and the Animal and Plant Health Inspection Service (APHIS) announced that they had made the permitting conditions more stringent. These requirements apply as of the 2003 season (USDA, 2003) and include the following:

- An increase in the number of field site inspections.
- For corn, no trial may be done less than 1 mile from another cornfield without controlled pollination or less than one-half mile from another field with controlled pollination.
- Restriction on producing food and feed in the year following a trial in a given field.
- Use of dedicated planters, harvesters and storage facilities.
- Non-dedicated equipment must be cleaned in accordance with APHIS-approved protocols.
- Seed cleaning and drying procedures must be approved.
- An approved training program for personnel involved in trials must be implemented.
- The size of the perimeter fallow zone around the field trial is increased from 25 to 50 feet.

In addition to these changes, APHIS is soliciting comment from the public on three questions:

- What additional measures can APHIS take or employ to increase transparency and enhance the flow of information to interested parties and the public?
- What alternative procedures, including the scientific data and technical rationale on which these alternative procedures are based, could be used for ensuring adequate confinement for field trials?
- What methods or approaches should APHIS utilize to ensure compliance?

In the United States, a company wishing to conduct a field trial must submit a report to APHIS containing at least the following: general information on the crop, the gene, the trial site and the manner in which it will be used, the trial start and end dates, and the

manner in which the crop will be destroyed after the trial.[10] From 1991 to 2002, approximately 198 field trial permits were issued for areas ranging from 1 to 40 acres. APHIS does not currently limit the trial area and it is possible that individual trials will grow to hundreds of hectares in the coming years (Freese, 2002). The principal plants used in field trials are corn, soy, rice, and tobacco for production of vaccines, contraceptives, growth hormones and industrial enzymes. The states that account for the bulk of the trials are Nebraska, Wisconsin, Maryland, Kentucky, Texas, Hawaii, Puerto Rico, Iowa, Illinois, California, Indiana, and Florida. In 2002, about 300 acres of land were devoted to molecular farming experiments.

The USDA does not divulge the exact location of field trials but does reveal the state name. The situation is similar to Canada, where only the province name is revealed. This practice is different from that of other countries. For example, in England[11] and Australia, the public has access to a register containing the exact trial locations (Reuters, 2001).

This confidentiality issue can be looked at in different ways. On the one hand it might be surmised that the purpose of this practice is to prevent farmers from ascertaining whether a trial is taking place near their land as well as to prevent independent scientists from evaluating the data submitted in support of permit applications. On the other hand, the practice might be intended to prevent groups and individuals who are categorically opposed to GM crops from destroying the trials.

3.1- The Prodigene Incident

The molecular farming guidelines implemented by the USDA and the FDA in March 2003 (stricter permitting conditions for field trials) were drafted after an incident caused by the U.S. company Prodigene Inc. According to a recent Reuters article (Gilliam, 2002) this Texas-based leader in molecular farming violated the US guidelines. In Nebraska, Prodigene contaminated soy seeds for human consumption with GM corn seeds

[10] Permit application forms are available at http://www.aphis.usda.gov/biotech .
[11] GeneWatch, 2001. "GM crops currently being field trialled in the UK." GeneWatch UK, which contains grid map coordinates for all GM field trials. See http://www.genewatch.org/Home.htm.

biopharmed to treat diabetes and diarrhea in pigs. The experimental corn crop had been grown the previous year in the same field. The transgenic corn was detected through testing of the soy silos. Prodigene was fined $2.8 million and ordered to destroy 15,000 tons of contaminated soy.

This incident provoked sharp reactions from certain groups. The Biotechnology Industries Organization (BIO)[12] declared a moratorium on growing transgenic plants for pharmaceutical or industrial purposes in those states of the Corn Belt where corn is grown for human consumption (Iowa, Illinois and Indiana). It justified the moratorium based on the insufficiency of existing data on this type of production and the possibility of contaminating the food chain, through cross-contamination among other factors. However, BIO reversed itself after the new, more stringent guidelines were issued. BIO recently supported FDA and USDA initiatives to develop molecular farming guidelines.[13]

The incident caused concern among environmental organizations and consumers. Molecular farming opponents such as Friends of the Earth accused Prodigene of having improperly confined its crop and asked the US government to ban molecular farming, or at least to exclude corn as a potential biopharmed crop. Other groups are demanding that molecular farming only be carried out under strict confinement (greenhouses, mines) and only with plants not intended for food or feed, such as tobacco (Kamenetsky, 2003).

Two other US companies, Pioneer Hi-Bred and Dow AgroSciences, were fined less than $10,000 each by the US Environmental Protection Agency (EPA) for having improperly confined experimental corn crops producing medically useful biomolecules and for failing to take the necessary steps to prevent pollen drift to neighbouring fields.

[12] BIO represents more than 1,000 biotechnology companies, academic institutions, and biotechnology centres in all 50 US states and some 33 other countries. The organization's members are involved in research and development in the fields of health protection, agriculture, and biotechnology products for industry and the environment. For more information, see: http://www.bio.org .

[13] For more information, see http://www.bio.org/pmp .

4.0 PMF Regulation in France

In France, plants intended for molecular farming are considered to be no different from any other transgenic plant and are reviewed on a case-by-case basis. Applications for trials in confined spaces (greenhouses, laboratories) are filed with the Commission du génie génétique (CGG), a body of the Ministry of Research. Field trial applications are submitted to the Commission du génie biomoléculaire (CGB), an appointed body composed of scientists, environmentalists, health specialists and consumers whose mission is to assess the public health and environmental risks linked to GMO release. The CGG and the CGB are advisory bodies with no decision-making power; it is up to the Ministry to grant certification or authorization. The CGB reviews files and advises the Ministry of Agriculture, Food, Fisheries and Rural Affairs[14] as well as the Ministry of the Environment and Development, which decide whether or not to authorize the trial. They may recommend confinement measures (isolation distance, etc.), which may be adopted as is or modified by the Ministry. The CGB bases its decisions, *inter alia,* on the characteristics of the trial, its location and biotope, and the characteristics of the introduced gene sequences. The Ministry of Agriculture bases its decision on European Community Directive 2001/18/EC on the deliberate environmental release of GM organisms, in particular for purposes of medical research (Part B applies to field research and Part C to commercial production). The Ministry of Agriculture publishes its decision in the form of public information forms on its website at http://www.agriculture.gouv.fr. The public information procedure is mandatory for all deliberate releases of transgenic plants. However, only the names of the communes in which the trials are conducted is posted on the Internet. The land registry references are not revealed.

The European Agency for the Evaluation of Medicinal Products (EMEA) has responsibility for the assessment of drugs in general, including those derived from GM plants. Developers must register drugs with the EMEA. As do conventional drugs, these drugs undergo a panoply of clinical trials to assess their quality, safety, and efficacy.

[14] For more information on this ministry, see: http://www.agriculture.gouv.fr .

The Ministry of Agriculture's website states that commercial production of plant-based pharmaceuticals can be expected within five to ten years.

5.0 Reasons for PMF

5.1- History of GMO-Based Pharmaceutical Production

In the 1970s, protein-based drugs were available in only limited quantities. Since then, pharmaceutical proteins and industrial enzymes have been produced primarily from GM bacteria. The first GM pharmaceuticals were insulin and interferon, produced from the well-known bacteria *E. coli*. The advantage of this bacteria is that it reproduces a large quantity of recombinant proteins rapidly and cheaply compared to fermentation. However, the bacteria cannot produce molecules as complex as those produced by yeast and insects. Bacteria no longer suffice for the needs of recombinant protein production.

5.2- Advantages of PMF

PMF is perceived as a viable alternative for the production of biopharmaceuticals. Conventional drug production methods are limited by their excessively high costs.

The following are the main conventional drug production systems (Daniell, 2001):

- Mammal cells modified through the use of recombinant DNA techniques, the advantage being that the compounds produced are identical to the original ones. This method is costly and the scale of production is limited.
- Microorganisms (e.g., bacteria), which have the disadvantage of producing compounds that vary greatly from the original product.

Cell cultures and bacterial fermentation are the technologies most frequently used in the production of therapeutic proteins. Antibiotics are often produced by bacteria while monoclonal antibodies and the majority of vaccines are produced by mammal cells. The

last stage of production in animal cells is that of glycosylation, or the addition of sugars to the protein so that it bends in a specific way. The bending angle determines the protein's function and whether it is active or not. Proteins not requiring glycosylation are produced in bacterial fermenters, while others are produced by mammal cells.

In recent years, protein-based methods for drug production (e.g., use of Chinese hamster ovary cells) have plateaued. These processes are not cost-effective for certain applications. The pharmaceutical industry urgently needs proteins in order to develop safe and effective drugs, but its production capacity is limited. Research on certain drugs might even be abandoned. The conventional cell culture method for biomolecule production demands a great deal of energy, space and investment. In short, the pharmaceutical industry is unable to meet the demand for protein-based drugs (Felsot, 2002). For example, the US-based firm Immunex is having considerable difficulty procuring an adequate supply of Embrel,® a drug used in treating rheumatoid arthritis. Cell-based production levels of Embrel® are insufficient, and the drug is becoming increasingly scarce and expensive. Plant-based Embrel® production has the potential to increase production volumes and lower costs. The Immunex case has induced numerous companies and countries to embark on molecular farming research (Lamoureux, 2002).

The table below summarizes the chief difficulties in drug production today and the solutions potentially represented by molecular farming.

Molecule	**Problem**	**Plant-based solution**
Hemoglobin	➢ Demand for blood is increasing, while the number of donors is decreasing ➢ Incompatibility of blood types ➢ Safety fears (HIV, VHC, VHB)	➢ Large-scale production ➢ No concerns regarding blood types ➢ No human pathogens
Antibodies	➢ Costly ➢ Limited production capacity	➢ Cost reduction ➢ Large-scale production

Embrel®	➢ Limited production capacity	➢ Large-scale production
Factor VII	➢ World shortage (only 40% of hemophiliacs have access to this product)	➢ Large-scale production: availability to all hemophiliacs
Insulin	➢ Too expensive for non-industrialized countries	➢ Cost reduction: accessibility to non-industrialized countries

Source: Presentation by Louis Vézina, Ph.D., of the company Medicago at the CFIA public forum on molecular farming in the fall of 2001.

The two main arguments put forward in favour of biopharming are decreased cost and product safety (Larrick et al., 1998; Fischer et al., 2001; Rogers, 2003). The main putative advantages of molecular farming are:

- Production of new pharmaceuticals for disease diagnosis and treatment.
- Cost-effectiveness in production of biopharmaceuticals, since unlike conventional production, cell culture fermentation systems and bioreactors are not required (lower capital investment). In addition, production can take place on a much larger scale.
- Proteins are produced in intracellular compartments of the plant, so they are more stable. As well, they can be directly expressed in certain plant components such as chloroplasts.
- Safe production, since there is no transmission of toxins or pathogens to humans. The conventional method of extraction from animal tissues poses the risk of contamination (viruses, prions).
- Plants with eukaryotic[15] cells offer the advantage of protein maturation more closely resembling that which occurs in human cells. The resulting proteins are practically ready to use. Bacteria can only produce simple proteins, but plants can synthesize much more complex glycoproteins. However, much work remains to be done on glycosylation mechanisms, whereby sugars are added by enzymes to the amino acid

skeleton. At this stage the biomolecules may become biologically inactive or immunogenic to human beings (Chevassus-au-Louis, 2001).

Although molecular farming appears advantageous for the production of certain pharmaceuticals, some biomolecules cannot be adequately synthesized in plant tissues.

5.2.1- A Carrot a Day: Eating Plants for Disease Prevention

Plants could be modified to serve as vaccines, delivering a large quantity of antigens at a low cost. They could be used to treat hepatitis, cirrhosis, cystic fibrosis, liver diseases, HIV, Gaucher's disease and hypertension. Several benefits are asserted for edible vaccines. Unlike conventional vaccines, in which weakened bacteria or viruses are injected into the body, edible vaccines directly administer the antigens that induce the immune system to produce antibodies. This means they would have fewer side effects. With no viruses and bacteria to be preserved, the production system for edible vaccines can dispense with cold chains, for a considerable cost savings. This would be beneficial for developing countries. Studies are currently attempting to freeze-dry certain biomolecules so that they can be administered in capsule rather than fresh food form (e.g., modified tomatoes and bananas). Vaccines under study include *Vibrio cholerae* and *E. coli*, two of the most widespread and deadly diseases in the developing world. But these vaccines are not yet ready for deployment (Mason et al., 1995). Before they can be put on the market, a number of issues must be resolved. Most important is a rigorous infrastructure for distribution and administration to the public in order to preserve their efficacy and safety (Fisher, 2000).

The National Institute of Agrobiological Sciences, Japan Paper Industries and the Sanwa Kagaku Research Institute have just completed development on a new rice variety containing a high level of a hormone, GLP-1, that helps the pancreas produce insulin.

[15] Eukaryotic cells are nucleated, whereas prokaryotic cells like those of bacteria have no nucleus.

This rice could be used in the treatment of diabetics and could be on the market within 2–3 years, depending on whether regulators and public opinion allows this to happen.[16]

5.3- Is PMF Profitable?

One of the main arguments in favour of PMF is its downward effect on costs. With PMF, costly fermentation systems are replaced by plants, making it possible to vary the scale of production. The biopharmaceuticals market is projected to reach US $140 billion by 2020 (Wired, 2002).

At present, PMF yields are still rather low. In order to be commercially viable, the concentration of the therapeutic protein must be at least 1% of the total protein produced. A recent review article describes levels 10 to 10,000 times lower than that threshold. (Daniell et al., 2001). One solution to this problem is for the proteins to be produced by chloroplasts, the photosynthetic plant cell organelles containing chlorophyll and DNA. If genetically modified, these organelles can reproduce up to 10,000 copies of a transgene in every cell, making it possible to attain the desired protein production levels. However, the use of chloroplasts has not been perfected for all PMF plants, and particularly the field crops of greatest interest.

Observers have adduced three reasons for believing that molecular farming will be unprofitable: 1) the purification of plant biomolecules will be too costly; 2) enormous sums will have to be invested to prevent cross-pollination (see section 7.1.2); 3) liability for contamination of conventional crops will add further costs.

Nevertheless, PMF appears to offer advantageous production costs even when the special costs related to molecular farming (e.g., yield, crop isolation) are factored in. A market survey conducted by the firm Planet Biotechnologies (Mountain View, California) found that the production of one gram of purified immunoglobulin A by a transgenic plant would cost US $50, as compared with US $1000 for current cell culture technology and US $100 for transgenic animals (Chevassus-au-Louis, 2001). This low cost is explained,

[16] Source: http://www.agrisalon.com/06=actu/article-10194.php .

among other factors, by the fact that molecular farming does not require major equipment such as fermenters. Extraction of the biomolecules from the plant would account for approximately 80% of the production costs of a recombinant protein. This step would cost no more or less than with conventional methods. At the end of the line, would drug prices to the consumer drop? The biotechnology industry seems to think so, and furthermore claims that consumers would have access to a wider variety of products.

The insufficiency of existing data makes it difficult to generalize about the commercial viability of molecular farming. Each application is different, and numerous variables have to be evaluated, including agronomic practices, effectiveness of gene expression, isolation requirements, health and environmental safety testing of the compound and plant, and ease of extraction and purification of the product. The possibility of usable molecular farming by-products such as oil or food would also have to be examined, and their market value appraised (College of Agriculture, 2002). For example, tobacco is different from soy, corn, and canola in that it produces a large quantity of green leaves per acre. This makes tobacco the most viable factory for pharmaceuticals that can be synthesized in leaves. But for biomolecules that must be produced in seeds, corn and soy are the best media, tobacco seeds being very small. Each crop has a unique genetic makeup and characteristics, and different production methods, and therefore the calculation of production costs is quite complex. The pairing of proteins with host crops will be determined by consideration of practical and economic factors including yields, storage conditions, confinement issues, production costs, purification issues, market size, environmental issues and concerns, and public perception (Daniell et al., 2001).

RECOMMENDATION 4:

In view of the lack of adequate data on the commercial viability of molecular farming, Option consommateurs recommends that the CFIA conduct a study on its economic impacts, and more specifically on the cost of drugs derived from this technology.

6.0 Risks of PMF

As the foregoing discussion shows, molecular farming appears to offer economic advantages in drug production. However, it also poses risks to human health and the environment. Contrary to conventional laboratory methods, molecular farming can be carried out in open-air settings, leading to various potential consequences.

PMF is a relatively new technology. We still know very little about the effects of plant-based biopharmaceuticals on human health and the environment. The majority of research is still being done in laboratories, with only a few small-scale field trials. The problems associated with the first generation of transgenic foods, such as gene transfer between related species or cultivars, are just as pertinent to molecular farming.

6.1- Introduction of Biomolecules into Food, Feed, and the Environment

The possibility that biomolecules could be introduced into our environment is very real. As noted by Kirk (2001), the following are possible routes of introduction:

- Direct ingestion by mammals, invertebrates, birds, or other animals. Certain molecules may be bioactive at harvest time, others may not. Likewise, certain biomolecules may be destroyed by the digestion process but not others. These latter might wind up in the food chain.

- Breakdown of molecular farming residues in soil, root transpiration, and infiltration into water. This risk could be attenuated by targeting only aboveground plant parts as hosts for the biomolecule, a technically feasible solution.
- Pollen movement.
- Accidental mixing of biopharmed seeds with seeds for human consumption, e.g. at the handling or shipping stages. Seed dispersal from trucks is a more frequent contamination mechanism than pollen drift. The movement of agricultural machinery between fields is another source of dispersal. When production is done in the field, it is difficult to ensure that everything is kept clean and separate; the harvest always leaves residues and seeds in the field. It is illusory to imagine that farmers could biopharm for a biotechnology company without the risk of contamination, even if guided by strict specifications and robust systems of harvest segregation and traceability. Yet this is one avenue being explored by biotechnology companies.

RECOMMENDATION 5:

Given the excessive risk of contamination of the food chain by plant-based pharmaceuticals, Option consommateurs recommends that PMF not be performed by farmers under contract, but only by adequately trained biotechnology company staff.

6.1.1- Persistence of PMF By-Products in Soil

Some scientists contend that most biomolecules have a very short half-life[17] in soil due to bacterial activity. Taking the contrary view, a report by Friends of the Earth on molecular farming asserts these products to be quite stable in soil: "Even though biopharmaceuticals

are proteins, and therefore generally expected to break down more rapidly than synthetic drugs, several plant-grown insecticidal and drug proteins have been shown to have surprising stability" (Freese, 2002). However, certain plant parts, such as tobacco roots, do not survive the winter, making this crop a safer factory for biomolecules.

The CFIA is currently examining the advisability of having all molecular farming residues destroyed by incineration. It is not envisioning the use of this biomass in livestock feed or for other purposes. Fermentation of the residues for ethanol is a possible compromise, but this technique would contribute to the greenhouse effect. Ultimately, decisions on residue use will depend on the nature of the material and the risk it represents.

6.1.2- Pollen Movement

The spread of genetic material through pollen is raising considerable concerns. Scientists are attempting to develop isolation mechanisms to prevent pollen drift and cross-contamination. Various crop isolation techniques have been developed to limit the spread of genetic material.

6.1.3- Crop Isolation Techniques

6.1.3.1- Confined Production

Biopharmed crops may be produced in confined spaces such as greenhouses (specialized structures with barriers against pollen, insects, rodents, etc.), mines or caves. Cave production is a promising avenue that is starting to be developed in Canada and the United States. Crops might also be isolated in plastic tunnels. None of these techniques, though, offers a foolproof guarantee of hermetic containment. For example, these facilities are not proof against tornadoes, fires or floods. Even if total confinement is

[17] The half-life is the time during which the concentration of a product varies by a factor of two. The elimination half-life is therefore the time during which the concentration is reduced by one-half.

attained, contamination problems might arise at subsequent stages of production, such as shipping. Simply put, no technique can guarantee zero-risk.

6.1.3.2- Genetic Isolation

The goal of genetic isolation is to keep the pollen on the production site by techniques such as male sterilization, harvesting before flowering and pollen development, and insertion of genes into chloroplasts. Since pollen does not contain chloroplasts, the risk of contamination is diminished. Until now, this technique has worked only with tobacco and potatoes (Moller et al., 2003).

Another potential technique involves the use of inducible promoters. Promoters are genetic elements controlling the expression of the genes with which they are associated. Promoters may be induced by cold, heat, day length, chemicals, or other factors. They make it possible for a gene to be turned on at will.

Yet another technique involves the technology commonly known as "terminator genes": the genetic manipulation of plants to make the seed of the next generation sterile.[18]

6.1.3.3- Isolation Distances

Another isolation mechanism involves maintaining a safe distance between biopharmed and conventional crops. The CFIA, in its provisional amendments to Directive 2000–07, requires isolation distances two to four times longer than those required for PNTs in general, and it is particularly stringent in regard to plants that may enter the food or feed chain. But scientific knowledge about pollination over long distances is sketchy (New York Times, 2000). Different studies on canola pollen movement, for example, have reached different conclusions. A Scottish study found that 90% of canola pollen travelled no further than 360 metres, while a small percentage travelled up to 2.5 km. A French study found that 99.8% of pollen stayed within a 25 metre radius of the field. A 1998

[18] This technology was developed by the multinational corporation Monsanto.

Canadian study on large fields found that 98.5% of pollen remained in the field (Agrifood Awareness Australia Paper).

Two researchers, Daniel Skinner of Washington State University and Paul Saint-Amand of Kansas State University, worked on isolation distances for transgenic alfalfa (*Medicago sativa*), an insect-pollinated plant. They used an alfalfa variety that carries a rare natural molecular marker to track the pollen and found that the isolation distance must be at least 1,500 metres, although certain pollinators travelled over longer distances. These movements could not be detected because traps were not laid at those distances to capture the insects.

Following a six-year study, the Saskatoon Research Centre (Canada) concluded that genetic pollution linked to soy and rapeseed is now so significant that it is difficult to grow these crops conventionally or organically. The centre calls for a clear separation between zones. This point of view is shared by other scientists, such as Jeremy Sweet of the National Institute of Agricultural Botany in Cambridge. He states that this procedure is already used to prevent elite varieties of sugar beets and potatoes from being contaminated. The current standard distances in Canada between conventional and transgenic rapeseed are 175 m for seed production and 100 m for food or oil production (GE Newsletter, 2001).

In its report of 2001, the Royal Society of Canada comment as follows: "A major issue here concerns the issue of scale. Opportunities for gene transfer will be considerably greater for large-scale commercial plantings of GM crops than for small trial plots. Hence, generalizations about pollen dispersal distances of commercial planting based on experimental studies of small plots should be treated with some caution."

These results indicate that it is currently difficult to predict wind and bee borne pollen spread, hence any potential gene transfer and cross-contamination problems. Further study of this problem is necessary, indeed essential.

In short, the management of transgenic plants in general and those used in molecular farming in particular must take account of the risks of transgene spread to similar

cultivated and wild species. These risks in exist in natural populations when (Chèvre, 1997):

- The cultivated species is at least partially allogamous; that is, pollen from different individuals is required for fertilization.
- The pollen and/or seeds may travel over long distances.
- The same or related species are present spontaneously in the growing areas and flower during the same period.

It is possible to reduce the risks by using plants that lack these characteristics.

The CFIA claims that it takes a science-based approach in establishing isolation distances. However, it acknowledges that there are still gaps in our knowledge about the compatibility of PNTs, even if a great deal of information is available on the sexual compatibility of these crops with related wild species.

6.1.4- Impacts on Non-Target Organisms

Non-target organisms are defined as organisms present in the environment that are accidentally affected by a product. These organisms may be difficult to identify and study. The impacts of molecular farming on non-target organisms such as insects and soil microorganisms are not very well elucidated, and further study is called for. The level of risk to non-target organisms depends on the recombinant protein in question. The CFIA claims that most biopharmaceuticals that show characteristics are relatively inactive biologics such as vaccines and antibodies. Most of these substances are allegedly easily digestible and unlikely to be toxic. But there are concerns about the toxicity of some biopharmaceuticals (anticoagulants, hormones, and enzymes) at high doses as well as the persistence of others (lipophilic or fat-soluble compounds) in the environment. All biologics should be confined or isolated so as to prevent their environmental release. Strategies could include post-harvest inducible genes, product activation after purification, use of "terminator" genes to prevent pollen development, transformation of chloroplasts to limit gene flow, transgene tracking, marker proteins for specific

biopharmed plants, fluorescent proteins, buffer crops around biopharmed ones, greenhouse restrictions, etc.

6.2- Risks to Human and Animal Health

One concern raised at the CFIA consultations in the fall of 2001 was the possibility that livestock might eat molecular farming residues. At present there are no such residues in animal feed, since they are destroyed by incineration.

The following passage from the report describes how the participants at this consultation responded to the question on the evaluation of toxicity, allergenicity, and safety to humans and animals:

> Stakeholders were asked whether they felt that either toxicity and allergenicity assessments or full food or feed safety assessments should be made for products of plant molecular farming, as a requisite either for confined research field trials, for confined or unconfined commercial field production, or contained production. While products of plant molecular farming are not intended for use as food or feed, some stakeholders felt that full food or feed safety assessments should be required when the plant species used is a traditional food or feed crop, particularly for unconfined production. Other stakeholders felt that human and livestock health risk assessments may not be necessary for confined research field trials or commercial field production, depending on a case by case evaluation of confinement practices and of the risk of the product. Some stakeholders felt that a toxicity and allergenicity assessment would be adequate where such an assessment is required. Many stakeholders agreed that a human or livestock health risk assessment would not be required where production is in strict containment, provided there is confidence in the containment.

Certain scientists believe that there is no danger from ingesting small quantities of monoclonal antibodies or vaccines (which would be injected anyway), since these biomolecules would probably be digested before they enter the bloodstream. But even if so, accidental contamination could create fears among consumers. The companies involved in molecular farming have every interest in isolating their products so that residues are kept out of food and feed.

Given the major concerns raised by biopharmed plants in regard to human and animal health and the environment, it seems likely that these would be barred from unconfined release, i.e., release without reproductive isolation. Some observers even contend that biopharmed plants should be limited to those not used as food or feed, and that they should be grown under strict confinement:

> In a submission to the Canadian Biotechnology advisory committee, genetist and biochemist Dennis R. McCalla and colleagues point to the potential health impacts from inadvertent consumption of plant-grown vaccines, stating that there is a "very high probability that plants engineered to produce pharmaceuticals, enzymes and industrial chemical" will contaminate the human food supply. "Only species that are not consumed by humans or by livestock should be permitted for the production of these substances." The Genetically engineered food alert coalition agrees, and recommends that only contained, non food alternative to open-air biopharming be allowed (McCalla, 2001).

6.2.1- Health Risks Posed by Biopharmed Drugs

Another concern raised by biopharmed products is their allergenic potential. This derives from the fact that the molecules added to proteins by plant cells during the process of glycosylation may be very different from those added by animal cells (Rogers, 2003). More research is needed on the human allergenic potential of these molecules. As mentioned above, it is necessary to ensure that the macromolecules produced from plants are biochemically, pharmacologically and clinically comparable to those, if any, obtained by conventional methods. A battery of physical, chemical, biological and immunochemical tests must be performed to compare products derived from humans and animals with those derived from plants. If differences are found, then pharmacokinetic studies become necessary (Miele, 1997).

6.3- CFIA Measures to Reduce the Risks of Field Trials

The CFIA recognizes that it is essential to do more research on the interactions between different species of plants, non-target organisms, and the environment. Considerable research has already been done on pollination behaviour and other characteristics. The

CFIA requires PNT developers to thoroughly characterize the chemistry, molecular biology, and expression of the new trait. The PBO states that in 2002 it authorized only confined field trials for plants posing little or no risk to the environment or human health.

For example, tobacco had no related sexually compatible species in Canada and the field trials were carried out thousands of kilometres away from commercial tobacco crops. Furthermore, the tobacco plants were harvested before flowering to minimize pollen drift. Deer fencing was erected around the fields to prevent intrusion by mammals, whose digestion could be affected by the active compound in the plant. Similarly, safflower has no sexually compatible wild species and the trials were carried out at distances at least four times longer than the normal isolation distance for commercial production. There was no safflower production in the trial province, Alberta. Here too, deer fencing was installed around the field trials. These two trials were inspected by the CFIA during the growing season and during destruction of the residues. They were conducted on a very small scale at great distances from the habitats of endangered species. Finally, the compounds produced in both crops were inactive precursors to industrial and pharmaceutical products.

Following the fall 2001 consultation, the CFIA proposed regulatory measures for molecular farming:

- Explore containment standards.
- Explore "Safety Preservation" systems.
- Explore licensing requirements to control product movement.
- Require constant regulatory monitoring of plant molecular farming activities.
- Consider some plants not appropriate for molecular farming, based on biology and other factors.
- Require human/livestock toxicology/allergenicity or full food/feed assessment in some cases.
- Require that genetic mechanisms for confinement be verified prior to release.

- Develop protocols and procedures for environmental monitoring for accumulation in wildlife food chains, residual effects in soil and long-term effects.
- Expand the list of indicator species used to determine effects on non-target organisms.
- Establish mandatory Good Agricultural Practices.
- Require information on proposed hectarages of commercial production.
- Amend Regulatory Directive 2000–07 to provide for toxicity and allergenicity assessments by Health Canada and the Feed Section, CFIA for confined research field trials of food or feed crop plants producing pharmaceuticals, on a case by case basis.

This latter initiative was implemented by means of provisional amendments to directive 2000–07 on confined research field trials of PNTs for molecular farming:

- The use of major food or feed crop species for PMF is not recommended.
- The use of crop species that are pollinated by bees that contribute to commercial honey production is also not recommended for PMF.
- Developers are encouraged to consider fibre crops, crops with only minor food or feed use, small-acreage specialty food or feed crops, or new crops as production platforms.
- The host species should also be as amenable to confinement as possible, i.e. developers should consider level of outcrossing, mode of pollination, weediness, seed dormancy, seed dispersal, harvest efficiency, tendency to volunteer, and available reproductive control mechanisms in choosing a host plant species.
- Genetic mechanisms such as tissue-specific or post-harvest inducible expression of the compound may be useful in mitigating environmental exposures.

RECOMMENDATION 6:

Option consommateurs recommends that more scientific research be done on molecular farming, more particularly on the issues related to long-distance pollination, gene transfer, and impacts on non-target organisms.

RECOMMENDATION 7:

Option consommateurs recommends that all production platforms be rigorously studied on a case-by-case basis before their environmental release and that isolation perimeters and strict physical and genetic confinement techniques be put in place.

RECOMMENDATION 8:

Given the risk of contamination of the food chain by biopharmed plants and the hermeticity problems of the current systems, Option consommateurs strongly recommends that food crops be excluded from the production of pharmaceutical biomolecules, except under strict confinement.

RECOMMENDATION 9:

To prevent contamination of food and feed, Option consommateurs recommends the development, without delay, of guidelines for robust identification and traceability systems for plants and products derived from PMF.

7.0 Views of Farmers and Consumers on PMF

7.1- Farmers and PMF

Some commentators think that molecular farming could open up new markets and provide supplemental income to farmers by resulting in contractual relationships with biotechnology or pharmaceutical companies. But not all companies involved in PMF are interested in such relationships; some prefer confined production. In fact, the choice greatly depends on the plant in question. Alfalfa, for example, is easily grown in greenhouses, while corn does better outdoors on larger plots.

The http://molecularfarming.com website presents what it sees as the advantages of molecular farming. It asserts that farmers' income, health and social well-being would be improved by this technology. In fact, the main purpose of this site is to gather the names of farmers who may be interested in renting their land, tunnels or greenhouses to pharmaceutical and/or biotechnology companies for trials and perhaps commercial production at a later stage. The farmer receives a price much higher than the market value of the land, and in exchange provides the machinery and the work. The site specifies that it is important for PMF to be done in countries where it is regulated and where farmers are sensitized and trained in this new form of agriculture. But the site also states that it would be important not to deprive developing countries of the advantages of molecular farming. After all, these countries need low-cost drugs. Farmers are promised that their

land will be rented at a price some twenty times higher than the normal price paid for food crops. The governments of Guinea, Sierra Leone and Mali have, in the medium term, approved molecular farming trials in their countries in the form of contracts with North American pharmaceutical and/or biotechnology companies.

But will farmers really benefit? The answer is unclear. It depends on a number of factors, such as the area devoted to molecular farming, the profit sharing arrangement between the firm and the producer, the feasibility of the production system, the required investments, the available government financial support, the necessary investment of time and money by the producer, the producer's liability in case of contamination, insurance issues, the producer's involvement in exporting, the producer's loss of independence, the potential impacts of molecular farming on the health of producers and their employees and, finally, the country's scientific, regulatory and administrative infrastructure.

In a straw poll of 340 farmers conducted at the American Farm Bureau Federation's annual meeting, nearly half (48%) of the respondents were opposed to or hesitant about molecular farming (Reuters, 2003). Of these 13% were categorically opposed, while 35% stated that they lacked information on the health effects of molecular farming and wanted to know more about it before going into production. Meanwhile, 50% said they would consider planting these crops.

7.2- Consumers and PMF

PMF is attracting increasing media attention and arousing fears and questions among the public. The fact is that molecular farming uses genetically modified plants, and the controversy around GMOs is of course well-publicized. Molecular farming differs in that its products are not intended for food or feed, but this argument does not satisfy everyone — especially not those opposed in principle to the use of genetic engineering to manipulate living organisms.

Consumers International (an international organization advocating for consumers' rights) has posted on its website a sample letter to various US authorities including the USDA

asking them to ban biopharming outright.[19] More specifically, the letter calls for an immediate moratorium on all production of biopharmaceuticals and industrial chemicals in food crops in the United States, including field trials.

7.2.1- Results of PMF Focus Groups

In order to ascertain Canadian consumers' level of awareness about PMF and their opinions on its risks and benefits, Option consommateurs commissioned the firm Environics to conduct a series of focus groups on PMF in February 2003. The focus group report follows.

[19] For more information, see the Consumers International site at http://www.consumersinternational.org .

7.2.1.1- Environics Research Report

Focus Group Report to

Option consommateurs on

Public Attitudes Toward

The Issue of Molecular Farming

February, 2003

PN 5302

Environics Research Group Limited

I. EXECUTIVE SUMMARY

Modern science has continued to explore and open up new frontiers with gene science. The scientific advancement that has resulted from research into the genetic and molecular structures of nature has given humankind the means to genetically modify the properties of food and genetically alter plants for the production of medicinal products. The science of genetically modifying plants for medicinal purposes has come to be known as molecular farming.

The focus groups that were conducted with participants in Toronto and Montreal on the topic of molecular farming produced a wide array of opinions and viewpoints. The major themes to arise out of the sessions were:

- **Previous Knowledge and Awareness of Molecular Farming is Very Low**

  The new gene science of molecular farming has yet to capture the attention of the public. Participants displayed little to no initial knowledge and awareness of molecular farming.

- **Participants Receptive to the Potential Benefits of Molecular Farming**

  Participants embraced the possibility that molecular farming could lower the production cost of drugs and perhaps discover cures to disease. Many confused it with natural health products and herbal remedies and thought it might produce more "natural" medicines with fewer side effects.

- **Participants Concerned About Molecular Farming's Potential Risks**

Participants expressed considerable concern that contamination of soil and water supplies could result from molecular farming. In addition, participants wondered what sort of short and long-term effects molecular farming would have on humans.

- **Molecular Farming Issue Important to Some, But Not to Others**

For some participants, the importance of molecular farming registers low on their scale of daily and global issues to keep in mind. Other participants viewed the molecular farming issue as important because of the unknown effects it will have on humans and the environment.

- **Molecular Farming's Benefits and Risks Difficult to Weigh At This Point**

With so much still unknown about molecular farming, participants could not determine whether the benefits or the risks were greater. Lack of research and information for the public cited as primary reasons for indecision.

- **Too Soon to Allow Commercial Molecular Farming**

Cognizant of the fact that molecular farming will continue to be explored, participants were very cautious about allowing Canada to commercialize molecular farming. Tightly controlled laboratories and greenhouses for molecular farming are acceptable at this point. There are reservations about the notion of open field farming being used in this way or of large crops being cultivated without further research and strict government regulations to ensure public and environmental safety.

II. PURPOSE AND METHODOLOGY

Environics Research is pleased to present this focus group report to Option Consommateurs. This report provides an overview of attitudes that Canadians hold towards the issue of molecular farming. In particular, levels of knowledge, fears and concerns, assessment of benefits and risks, and potential commercial use of molecular farming are explored in depth.

A series of four focus groups were conducted in February of 2003. Two were held in each of the following cities: Toronto (February 13th) and Montreal (February 15th). The participants in these focus groups were all recipients of a post-secondary education, aware of political and government issues, and interested in the topic of biotechnology and genetic modification.

The discussion guide used in the groups can be found in the Appendix at the conclusion of this report along with the briefing document that was provided to participants in advance of their session.

III. DETAILED FOCUS GROUP FINDINGS

A. Understanding and Awareness of Molecular Farming and Reaction to Discussion Piece

1. Understanding of Molecular Farming Discussion Piece

Virtually all participants in both cities gained a better understanding of molecular farming from the briefing document given to them in advance. Since the issue of molecular farming is relatively new, both in terms of public awareness and scientific advancement, previous knowledge of the issue was non-existent for most participants. However, having been introduced to the issue of molecular farming, participants raised questions about how far the technology has come and expressed concerns over its future impact.

2. Previous Awareness of Molecular Farming

With regards to previous information on molecular farming, the majority of participants in both cities had not seen, heard, or read anything aside from the briefing document provided to them. Some participants that were vaguely aware of molecular farming prior to attending the focus group mentioned that they might have seen an article in a magazine like Maclean's or viewed a show on the Discovery Channel. It is interesting to note that there was considerably more familiarity with the issue of GM foods. This perceived overlap of two gene science issues led to a certain level of confusion about molecular farming in the minds of participants. Furthermore, there was also an initial perception among some participants that molecular farming is designed to increase crop yields and make crops resistant to weather conditions or insects, though most understood it to be essentially genetic modification done for medical purposes.

A handful of participants in both cities were interested enough in the topic to have also visited the Canadian Food Inspection Agency website that was provided on the briefing document. For the most part, these participants read only the frequent asked questions portion and did not venture into the discussion document because they found it to be very complex and difficult to read. Some of the Montreal participants also complained that

while CFIA was supposed to be a neutral government agency, the website only described the benefits of molecular farming and said little about the possible risks and dangers.

B. Understanding of Molecular Farming and Related Fears, Concerns, and Questions

Participants were separated into pairs and asked to discuss and list all that they currently knew about molecular farming after having read the background materials. They were also asked to discuss and list what more they wanted to know about molecular farming.

1. Knowledge of Molecular Farming

Virtually all participants expressed knowledge of the fact that molecular farming aims to use plants for the production of pharmaceutical drugs. Most also noted that, by using GM versions of plants, the production of drugs could be a lot cheaper for consumers. However, while some participants were under the impression that molecular farming may lead to the discovery of cures for diseases, this was not mentioned as much as the potential for it to lead to cheaper drugs. Most participants also acknowledged the "element of danger" posed by accidental ingestion or exposure to molecular plants. In terms of commercial production, most participants were under the impression that this was a relatively new technology and that due to current government controls over research and production, commercial molecular farming is not being done in Canada at this time. Another issue raised by some participants centred on the need to more clearly differentiate the issue of molecular farming from the issue of GM foods.

2. Related Fears, Concerns, and Questions

While the participant's knowledge of facts about molecular farming were quite limited, their fears, concerns, and questions stemming from the issue were significant in volume and varied in nature. Virtually all participants cited environmental safety as their primary concern. Most participants raised questions about the impact that molecular farming would have on the water supply, quality of soil, and existing ecosystems. Additional environmental safety concerns raised by a number of participants related to harmful

effects resulting from possible cross-pollination between plant species and cross-contamination of food sources for wildlife. It is interesting to note that female participants more acutely expressed concern for the environment, while a number of male participants were of the opinion that molecular farming is simply another sign of technological progress that must inevitably be embraced.

Concern over the potential environmental impact led to concern over the impact that molecular farming might have on humans. Most participants expressed concern about how our human physiology would react to these molecular plants.

This concern over the "mixing" of our genes with molecular plants manifested itself in questions about possible allergic reactions and the long-term side effects of exposure. The increased incidences of asthma amongst children due to air pollution and cancer linked to asbestos were cited as examples where lack of caution and/or knowledge in the past has adversely affected society's current health. It was clear that many participants did not understand that the medications created through molecular farming would be chemically identical to the drug made by any other method. There was some misconception that this was about creating medications that were to be consumed as food. Some participants, in particular young females, said that perhaps increased emphasis should be placed on finding "natural" cures as opposed to the scientific pursuit of creating molecular plants for treatments of disease.

In addition to their concerns about the environmental and human impact, a number of participants raised questions about who will regulate and monitor molecular plant production, who is financing this research, and what the corporate goals are for molecular farming. Will biotechnology and pharmaceutical companies commit to producing cheaper drugs for consumers or is it simply about increasing profits? In other words, people wanted to know just who was going to be the beneficiary of the technology.

C. Importance of the Molecular Farming Issue

Opinion on the importance of the molecular farming issue was mixed. Most participants accepted the fact that molecular farming will inevitably be further explored and expressed concern about the future path of molecular farming. However, there was a general feeling

among participants, especially male participants over the age of 40, that that there are more pressing personal and global concerns than whether or not molecular farming should be pursued further. For some participants, in particular young females, the issue of molecular farming was viewed as very important because of the possible long-term effects that it could have on humans and the environment. Given their youth and long future ahead of them, these participants said that they want to ensure that the world they will leave future generations will be safe to live in. Some people mentioned zebra mussels or purple loosestrife as examples where humans "fiddled" with nature with disastrous results.

D. Exploring the Advantages and Disadvantages of Molecular Farming

1. Advantages of Molecular Farming

Virtually all participants agreed that the potential best things that could result from molecular farming were the possible discovery of cures for disease and the availability of cheaper drugs for consumers. Additional possible advantages cited by some participants included the development of better drugs with fewer side effects, improved societal health, and greater access to drugs for third-world nations resulting from lower drug costs. An interesting possible advantage that was raised spoke to the economic benefits of job creation resulting from the development of commercial molecular farming. Some participants in Toronto mentioned that this could be a new source of income for the hard-pressed farm sector.

It should be noted that a number of participants in both cities tended to confuse molecular farming and the medications it could produce with natural health products. Some were under the impression that this technology would be used to create herbal remedies as opposed to seeing it as a new way to create traditional medications that would be prescribed. As a result, some people thought that drugs derived this way might have fewer side effects because they were more "natural."

2. Disadvantages of Molecular Farming

Echoing the fears and concerns they expressed earlier, all participants cited possible long-term negative impacts on both humans and the environment as the most significant

drawbacks to molecular farming. Regarding the impact on humans, most participants voiced concern over the development of new diseases due to genetic mutations and the long-term effects that exposure to molecular plants will have on the human body. On an environmental level, most participants feared possible further environmental degradation, destruction of existing plant species, cross-pollination, and water or soil contamination. There were a number of participants who spoke of the risk of a bee pollinating a "medical plant" and then a non-medical plant, thereby spreading the medical agent to plants that would be sources of food.

Some participants, aware of the interest that biotechnology and pharmaceutical companies have in seeing molecular farming reach a commercial level, said that corruption of molecular farming by corporate greed was another possible disadvantage. There was a concern raised by some Toronto participants who worked in blue-collar jobs that there could be health risks for the people who would actually work with the plants that have been modified.

Virtually all participants cited safety concerns over ethical concerns when it came to their views on molecular farming. Some participants expressed having both ethical and safety concerns, but it was mainly safety concerns about the environmental impacts of potential accidents that preoccupied the participants. Only one participant unequivocally cited ethical concerns as being the foundation for their issues with molecular farming.

E. Weighing the Benefits and Risks Associated with Molecular Farming

Most participants, while acknowledging the delicate balancing act, could not conclusively decide whether the benefits of molecular farming outweighed the risks or vice versa. These noncommittal participants felt that between their lack of in-depth knowledge, lack of confidence that sufficient research has been conducted, and a sense that too much is unknown at this point, weighing the benefits and risks of molecular farming was simply too difficult to gauge at this point in time.

Some participants, in particular the male participants over the age of 40, clearly felt that the benefits of molecular farming outweigh its inherent risks. While cognizant of the risks involved, these participants subscribed to the notion that humankind needs to keep

moving forward and continue its progression into new areas of science. For these participants, the possibility of developing cures for diseases like cancer or discovering properties that would allow a quadriplegic to walk was more than enough to convince them that molecular farming could be beneficial to society.

Whereas many of the male participants embraced molecular farming's benefits, many of the younger female participants felt that the potential human and environmental risks might outweigh the benefits. Aside from the possible long-term human and environmental impact, these participants expressed a concern that our society is too dependent on the treatment of disease and not dependent enough on the prevention of disease. Citing the properties of rainforest plants and "old world" approaches to medicine, these participants felt a renewed emphasis should be placed on "natural" prevention. Some felt that "if we had not destroyed so many species in the Amazon rain forest that were possible sources of medicines, we would not have to resort to molecular farming in the first place."

In the minds of most participants, the issue of molecular farming is most closely linked with the issue of GM foods. A number of participants mentioned the issue of cloning as also being related to molecular farming, while a couple participants made reference to stem cell and embryo research.

All in all, there was no question that people find this particular form of biotechnology to offer far more potential benefits than they do in the case of GMOs that are more commonly discussed in the media. People have a hard time seeing how the benefits can outweigh the risks when it all seems to be about increasing yields or resistance to insects. In this case, it is a different story since the benefits could include life saving new drugs or drugs that could be made cheap enough to be accessible to more people.

F. Information Sources

1. Most Credible Information Sources

Virtually all participants stated that independent research scientists and independent scientific journals would be the most credible and trustworthy source of information regarding molecular farming. Some participants made mention of government bodies like

the Canadian Food Inspection Agency as being a "relatively authoritative source", while other participants said that they would seek a consensus from a variety of credible information sources.

2. Least Credible Information Sources

In considering the number of information sources for molecular farming, all participants were adamant in their distrust of any information source that has an interest in profiting from the development of molecular plants. Most participants mentioned biotechnology companies, pharmaceutical companies, and research scientists associated with these companies as lacking in credibility regarding information on molecular farming. Interestingly, some participants were "suspicious of government" and could not readily endorse the government as a credible information source.

G. Safe Molecular Farming for the Environment, Humans, and Wildlife

Overall, opinion as to whether molecular farming could be done in a safe way was mixed. A number of participants, noting the potential risk for accidents and humankind's other failed attempts to control nature, expressed reservations about whether molecular farming could be done safely with regard to the environment, humans, and wildlife. Younger female participants were most likely to share this cautious view. A similar number of participants felt that, given tight regulations and a controlled environment, safe molecular farming could be conducted. Mainly older male participants accepting of the science shared this view. Generally speaking, the consensus was that if the technology exists and experiments are being run then it is inevitable that molecular farming will be practiced. There was a concern that regulations not only be strict but also be enforced. Many people envisioned molecular farming as something that would happen in laboratories, greenhouses, and biodomes. It was clear that many people felt that special precautions would need to be taken if molecular farming was to be done in open fields. However, most people did think that it was possible for it to be done with minimal risk to the environment or to human health.

H. Future Direction for Molecular Farming

1. Commercial Applications

Most participants interpreted the commercial applications of molecular farming as farming done on a large scale and for profit. They tended to envision farmland or open fields of molecular plants and agreed that these fields would be "isolated", perhaps located in unpopulated areas. Some participants suggested that large greenhouses or biodomes would be a more likely scenario for commercial molecular farming.

While acknowledging that molecular farming could provide tangible benefits to consumers, most participants said that, between the risk of environmental accidents and the dearth of information on molecular farming's human and environmental impact, Canada should not open the doors to commercial molecular farming at this time. They cited the need for more research studies and "proof of benefits" before they would be willing to consider the idea of commercial farming.

Some older male participants, expressing their belief in scientific progress, encouraged Canada to further explore the idea of developing molecular farming into a commercial enterprise.

Virtually all participants stated that, should commercial molecular farming be allowed, strict government regulations and tight monitoring would have to be in place. Some participants felt that initial attempts at commercial molecular farming should be conducted in greenhouses only and not open fields. Citing the lack of public awareness of molecular farming, some participants cited the need for more public disclosure as another condition of allowing this science to be commercialized.

2. Confidence in the Canadian Food Inspection Agency

Almost all participants expressed confidence in the ability of the Canadian Food Inspection Agency to set regulations on molecular farming. Some participants cited a perception that the agency has a long track record of protecting consumers as the reason for their confidence.

However, most participants expressed doubt as to whether the Canadian Food Inspection Agency could adequately enforce their regulations and felt that federal law enforcement bodies should be involved to ensure that regulations are being followed. There was also some sentiment expressed, particularly in Montreal, that as a government agency, the CFIA might be unduly influenced and lobbied by drug companies.

APPENDICES

FEBRUARY 10, 2003

DISCUSSION GUIDE

ENVIRONICS PN 5302

MOLECULAR FARMING

1.0 INTRODUCTION TO PROCEDURES (5 MINUTES)

Welcome to the group. We want to hear your opinions. Not what you think other people think — but what you think!

Feel free to agree or disagree. Even if you are just one person among ten that takes a certain point of view, you could represent hundreds of thousands of people in the country who feel the same way as you do.

You don't have to direct all your comments to me; you can exchange ideas and arguments with each other too.

You are being taped and observed to help me write my report.

I may take some notes during the group to remind myself of things also.

The hostess (I) will pay you your incentives at the end of the session.

Let's go around the table so that each of you can tell us your name and a little

bit about yourself, such as what you do for a living, who lives in your house and what you like to do for fun.

2.0 INTRODUCTION TO MOLECULAR FARMING AND FINDING OUT WHAT THE PARTICIPANTS MAY KNOW ABOUT THE ISSUE (15 MINUTES)

As you probably guessed from the information sheet we had you read in advance, tonight we are going to be talking about the issue of molecular farming and agriculture.

Did this document provide you with a better understanding of what molecular farming is all about?

Before you looked at that document, had you ever seen, heard, or read anything before about molecular farming? What had you heard about molecular farming?

Where or who did your information come from?

Did anyone visit the (Canadian Food Inspection Agency) website mentioned in the document for more information on molecular farming?

3.0 IMPORTANCE OF MOLECULAR FARMING AND FINDING OUT WHAT FEARS, CONCERNS, AND QUESTIONS THE PARTICIPANTS MAY HAVE ABOUT THE ISSUE (25 MINUTES)

At this point I would like to break the group up into pairs and give you a little assignment. I'll distribute some paper and markers for you to write with.

For the next few minutes, I would like for you and your partner to discuss what you know about molecular farming and what fears, concerns, or questions you have about molecular farming.

Down the left-hand side of your paper, write down all that you know about molecular farming.

Down the right hand side of your paper, write down any fears, concerns, or questions you have about molecular farming. In other words what do you want to know about it?

Please put your paper up so that we can all see it and let us know what you and your partner's thoughts are about molecular farming. And for each point you have, please tell us your thinking behind what you wrote down…why it matters to you. Please feel free to take turns sharing your thoughts.

Then explain to the group what it is about molecular farming that you want to know more about.

How important is this issue to you?

What is it about molecular farming that makes this issue important or unimportant to you?

4.0 EXPLORING THE BENEFITS AND RISKS OF MOLECULAR FARMING

(20 MINUTES)

What do you see as the possible advantages of molecular farming? What are the potential best things about it?

What do you see as the possible disadvantages of molecular farming? What's the worse that could happen?

Knowing both the advantages and disadvantages, do you think that the benefits of pursuing molecular farming outweigh the risks involved or are it the other way around?

What is the primary reason why you think the benefits of molecular farming outweigh the risks?

What is the primary reason behind why you think the risks outweigh the benefits?

5.0 CREDIBLE INFORMATION SOURCES

RELATIONSHIP OF MOLECULAR FARMING TO OTHER ISSUES

ETHICAL CONCERNS VS. SAFETY CONCERNS

(20 MINUTES)

As you can imagine, there are a number of sources from which you can get information on molecular farming. Sources of information include the federal government, environmental organizations, research scientists, agricultural organizations, biotechnology companies, consumer rights organizations etc.

Who do you feel would be the most credible or trustworthy source of information on molecular farming? Why?

Who do you feel would be the least credible source of information on molecular farming? Why?

In your mind, is the issue of molecular farming related to any other agricultural and/or gene science issue? What issues would those be?

Does the issue of molecular farming concern you more from an ethical point of view…(i.e.: the notion of playing God with nature)…or does your concern stem more from an safety point of view…(i.e.: if wildlife comes into contact with a molecular farming crop etc…)

Why?

Can you see molecular farming being done in a safe way for the environment, humans, and wildlife?

6.0 FUTURE DIRECTION FOR MOLECULAR FARMING (30 MINUTES)

At present, molecular farming is being conducted in highly/tightly controlled government laboratories on an experimental basis. If molecular farming were to be done on a commercial basis, what does commercial mean to you?

Probe: What commercial applications come to mind? (greenhouses, crops, etc.)

Do the commercial applications you are speaking of bring to mind any additional concerns?

After all that we have discussed in the last 90 minutes, should Canada explore allowing molecular farming to be done on a commercial basis?

Under what conditions would you allow molecular farming to be done commercially?

What sort of regulations should be in place for commercial molecular farming?

Currently, the Canadian Food Inspection Agency will set any regulations for commercial molecular farming. Do you have confidence in their ability to effectively set regulations?

Can you think of any other organizations/associations that you would feel confident in to set regulations for commercial molecular farming?

THANK YOU FOR YOUR PARTICIPATION

What is PMF?

To be read in advance of focus group discussion

PMF is described as using plants in agriculture to produce biomolecules instead of foods and textile fibres. It means attributing "novel traits" to these plants through genetic change. These PNTs produce biomolecules that are of scientific, medical or industrial value. Plants therefore become pharmaceutical factories of sorts. This discussion group focuses more precisely on medical products that can be manufactured from these GM plants.

Research is currently underway with tobacco plants, which produce interleukin-10, a therapeutic protein used to treat Crohn's disease. Other plants can be used to manufacture therapeutic antibodies and diagnostic tools, which for example can help prevent cavities, avert organ rejection following a kidney transplant and fight breast cancer.

Manufacturing medications by using transgenic plants has certain advantages. Production costs are greatly reduced because plant farming requires less equipment and the process is safer. Indeed, plants rarely carry viruses or other infectious agents that are transmissible to humans.

In Canada, molecular farming has not been used for commercial purposes so far. Research is currently underway in greenhouses, in laboratories or in confined field trials (reproductive isolation), under the supervision of the Canadian Food Inspection Agency (CFIA). No medication made from these plants has yet been marketed.

The Canadian Food Inspection Agency is in charge of regulating PNTs, such as those used in molecular farming. The Agency is aware that molecular plant farming can be hazardous to human and animal health as well as to the environment. These hazards include the following:

Risk of inhalation or topical exposure for those who work with these plants;

The mixing of molecular farming products with those destined for human or animal consumption, which would result in accidental ingestion;

Accidental grazing by livestock of molecular farming crops;

Risks associated to an inappropriate disposal of plant biomass waste;

Emotional reaction to the use of human genes in food crops.

To reduce the potential risk of any negative impact, the CFIA suggests the following initiatives:

That crop isolation standards be carefully studied;

That methods be studied and implemented to ensure continuous security;

That any authorizations that are given also ensure the monitoring of product transportation;

That the regulations surrounding molecular farming activities be constantly monitored;

That certain plants that are not suitable because of biological factors or other reasons be segregated and put elsewhere;

That the toxicity and risk of allergy for humans or livestock be determined and foods used by humans and animals be thoroughly evaluated;

That genetic isolation mechanisms be verified before the environmental release of the plants;

That protocols and guidelines be developed to control the following elements in the environment: any accumulation of organisms in animal life food chains, the residual effects in the soil and long term effects;

That to measure the impact of this technology we study what it does to other non-target organisms such as those existing in the soil

That proper and compulsory farming practices be implemented;

That information relating to the surface areas submitted for commercial use be provided;

That the 2000–07 regulatory directive relating to controlled field trials for research purposes be modified. This will enable a case-by-case assessment of the toxicity in plants and/or the risk of allergy to plants that are destined for human or animal consumption and that are grown by Health Canada and the Feed Section of the CFIA for the purpose of manufacturing pharmaceutical substances.

For further information on molecular farming, please go to the following website:

http://www.inspection.gc.ca/english/plaveg/pbo/mf/molecule.shtml

RECOMMENDATION 10:

Given the lack of publicly available information about plant molecular farming and the concomitant lack of consumer knowledge of the issues, Option consommateurs recommends that the Government of Canada implement an information strategy based on the latest work in the field of PMF.

RECOMMENDATION 11:

Option consommateurs recommends that the information provided to the public by the Government of Canada on molecular farming be evaluated by an independent interdisciplinary committee before being made public.

RECOMMENDATION 12:

Option consommateurs recommends that the public agencies whose mandate is to provide scientific information to the public, such as the Conseil de la science et de la technologie du Québec, be involved in a public information and awareness strategy on plant molecular farming.

Conclusion

Like any new technology, molecular farming presents both risks and benefits. Do the latter outweigh the former? Some say yes, arguing that lives could be saved; others say no, arguing that the risk of contaminating the food chain and the environment is too great. Is the public willing to run certain risks in order to take advantage of molecular farming? It appears that consumers currently lack the information necessary to assess the situation adequately. The prospect of having access to a wider range of cheaper drugs is attractive to many, but not at any cost. Consumers are particularly concerned that traces of biopharmaceuticals could wind up in their food. They want to be certain that governments are taking the utmost precautions to prevent such contamination. They are not at all comfortable with the idea of open-air biopharming over a large area. They see confined production as being a more appropriate approach.

The products of PMF are, of course, not intended for human food consumption. Like conventional drugs, these products will be packaged, prescribed, sold and administered. Open-air or confined PMF would require the implementation of robust traceability systems and rigorous tracking of plant and product identity from field to medicine chest. It would also be necessary to establish good agriculture and agronomic practices as well as standard operating procedures (handling, shipping, harvest). Finally, regulatory agencies would have to audit biopharming operations.

In brief, the PMF industry and the government have many challenges to meet. They must guarantee the safety of PMF crops for human and animal health and minimize the negative environmental impacts. As well, they will have to publicize this new practice and be attentive to public concerns and questions. The implementation of clear, transparent, science-based regulations as well as a robust surveillance system are essential. The CFIA consultation process and public participation should also continue.

In conclusion, whether we agree, totally disagree, or somewhat agree with this new technology, PMF seems to be here to stay and will probably grow. It is crucial that this

development not take place at the expense of human and animal health and the environment. It is up to the industry now to prove to the public that PMF has advantages where drug production is concerned and that the risks are fully under control.

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